APB recognition region present in a first protein and an APB domain present in a second protein, wherein said APB domain shares at least 75% sequence similarity or at least 80% sequence identity with the APB domain present in amino acids 46-209 of $p52^{shc}$ as set forth in SEQ ID NO:2.

31. (Amended) The method of claim 26, wherein said first protein is a receptor tyrosine kinase.

REMARKS

Claims 26-32 and 35 are pending. Claim 26 is amended to recite a specific portion of an APB domain. Support for this amendment is found on page 5, lines 11-14, page 13, line 28 to page 14, line 21, page 25, lines 1-6 and Figure 4. Applicants wish to point out that claim 26 defines a specific portion of an APB domain as claimed in parent application serial number 08/363,215, now U.S. Patent No. 5,807,989. Claim 31 is amended to properly depend from claim 26.

Claim Rejections -35 U.S.C. § 112, Second Paragraph

Claims 26-35 remain rejected by the examiner under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants again respectfully request reconsideration and withdrawal of the rejection.

The examiner asserts that the term "therapeutically effective amount" in claims 26-35 is a relative term which renders the claim indefinite. Applicants respectfully disagree and direct the examiner's attention to page 8, lines 18-21 of the specification where the term "therapeutically effective amount" is defined in regard to inhibiting cell growth or proliferation. Further, page 46, line 7 to page 47, line 16, provide guidance to determine a therapeutically effective dose by obtaining data in cell culture assays and animal studies which can be used to formulate a range of dosage in a human. Additionally, on page 49, line 27 through page 50, line 2 of the specification it states "[d]etermination of the effective amounts is well within the capability of those of ordinary skill in the art, especially in light of the detailed disclosure provided herein." The claims requires a "therapeutically effective amount" which decreases binding between an APB recognition region and an APB domain.

Therefore, the term "therapeutically effective amount" would not be considered unclear by a person of ordinary skill in the art.

The examiner also asserts that the term "agent" in claims 26-35 is not clear. Applicants respectfully disagree and direct the examiner's attention to page 6, lines 7-9 where therapeutic agents are described as "agents able to modulate APB mediated activity between proteins and, thus alter signal transduction." Further, agents are described on page 10, lines 3-15, particularly in lines 12-15. Additionally, applicants direct the examiner's attention to page 23, line 26 through page 33, line 7 where the agents encompassed by the present invention and methods for identifying such agents are described. Further, the claim recites that the agent decreases the binding between an APB recognition and an APB domain. Therefore, the term "agent" would not be considered unclear by a person of ordinary skill in the art. Applicants have added the term "therapeutic" to make it clear that "therapeutic agents" are intended. This amendment is supported as noted above.

Claim Rejections - 35 U.S.C. § 112, First Paragraph

Claims 26-35 remain rejected by the examiner under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. Applicants respectfully request reconsideration and withdrawal of the rejection.

The examiner asserts that the term "APB domain" is broadly defined in the specification as having at least 20% sequence identity to the APB domain present in Shc and plays a role in signal transduction. The Examiner contends that this definition of the APB domain encompasses a large number of proteins. Applicants have amended claim 26 to recite "wherein said APB domain shares at least 80% sequence identity or at least 75% sequence similarity with the APB domain present in amino acids 46-209 of $p52^{shc}$ as set forth in SEQ ID NO:2," which more clearly defines the APB domain. Support for this amendment is found in the present specification as noted above. Thus, it is believed that the rejections based on the breadth of the APB domain are moot.

The method of amended claim 26 is enabled because a person of ordinary skill in the art would be able to identify an APB domain that shares at least 80% sequence identity or

at least 75% sequence similarity with the APB domain present in amino acids 46-209 of $p52^{shc}$ as set forth in SEQ ID NO:2 using techniques readily available to those of skill in the art.

The Examiner states that the use of the term "altering" encompasses both enhancing and decreasing signal transduction but applicants point out that the language of the body of the claim recites that the therapeutic agent decreases the binding between an APB recognition region and an APB domain. This language functionally defines the effect of the agent. The term "agent" has been amended to "therapeutic agent" which is defined in the specification.

The examiner asserts that no other APB recognition regions are taught or suggested, other than the exemplified EGFR, HER2/neu and TrkA. Applicants respectfully disagree. The APB domain has been identified as a specific sequence, and thus, other APB recognition regions to which the claimed APB domain binds can be readily identified by one of ordinary skill in the art. Therefore, the present specification does teach and suggest molecules containing an APB recognition region, other than the exemplified EGFR, HER2/neu and TrkA. In regard to claims with subject matter to these specific regions, the examiner is directed to claim 35 which is directed to these specific APB recognition regions.

The examiner asserts that sufficient evidence is not provided to support a role for APB binding in the mediation of signal transduction. Applicants respectfully disagree. The present invention concerns a domain in the amino terminus of Shc that is implicated in tyrosine kinase-mediated signal transduction, and the claim clearly recites this region. The domain is distinct from the SH2 domain and represents a newly elucidated mechanism of protein interaction with growth factor receptors and other tyrosine-phosphorylated proteins. This amino terminal domain is shown to cooperate with the SH2 domain to promote binding to growth factor receptors. The nature of the invention thus has importance in signal transduction, particularly tyrosine kinase systems, and specifically in modulating signal transduction of such systems.

The examiner continues that in vivo therapy is experimental and unpredictable and asserts that no cells are treated. Applicants refer the Examiner to the examples beginning on page 57 that cells were grown and lysed and contacted with GST fusion proteins and binding was assessed. Thus, if binding can be assessed then the effect of a therapeutic agent on binding also can be assessed. The results in in vitro assays lead scientists to studies in animals and then in humans. Applicants submit that in vitro studies are predictive of the outcome in vivo.

Applicants submit that the present specification provides sufficient enablement for the present method, as amended. It is well known in the art that molecules that disrupt the RAS-MAPK pathway are useful for treating cancer. The specification, at page 23, lines 10-25, identifies the binding of the APB domain of Shc to GRB2/SOS in the activation of the RAS pathway. In addition, as discussed in the left panel on page 231 of Luschnig, et al. *Molecular Cell* **5** 231-241 (2000), previously submitted, receptor tyrosine kinases activate the RAS-MAPK pathway. Luschnig et al. also state that mammalian SHC acts as an adaptor to link receptor tyrosine kinases via GRB2 to RAS activation (see page 231, right panel). Since molecules that disrupt the RAS-MAPK pathway are known to be useful for treating cancer, agents that decrease the binding between the APB binding domain of SHC and the APB recognition region of a protein that binds to SHC, should be useful for treating cancer. Therefore, the *in vitro* assay provided in the present specification is a good predictor of compounds that would be useful in the treatment of cancer. The examiner is respectfully referred to the Court of Appeals for the Federal Circuit's decision *in In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications.

Beginning on page 44, line 16 is a further section entitled "Diagnosis." This section continues through line 5 of page 46 and describes how protein complexes involving APB binding may be utilized in the prognostic evaluation of the condition of a patient suspected of exhibiting an APB affiliated signal transduction disorder. Further, on page 46, line 7 is a section entitled "Administration." This section describes how agents that modulate APB activity can be administered to a patient using standard techniques such as determining the

LD_{50} and the ED_{50}. Page 47, line 17 et seq. describes how one of skill in the art possessed with knowledge such as found in Fingi et al. (1975) "The Pharmacological Basis of Therapeutics," Chapter 1, can put to use the invention for treatment. And, again, on page 48, line 11 is stated that resort may be had to "Remington's Pharmaceutical Sciences," 1990, 18th ed. Mack Publishing Co., Easton, PA, for various routes and modes of administration. See, e.g., page 52, line 8. Remington's is an extremely thorough and well-respected treatise on pharmaceutical formulations.

It is noted that in the outstanding Office Action, the examiner raises specific "clinical" concerns with respect to the suitability of using the present method *in vivo*. Applicants assert that these types of concerns are more properly addressed by other government bodies, such as the FDA, and are therefore outside of the scope of the USPTO. The present application meets the USPTO's requirements for enablement. The clinical suitability of the present method for use *in vivo* is a question to be addressed by government bodies other than the USPTO. The present examples illustrate binding between an APB recognition region present in a first protein and an APB domain present in a second protein. As discussed above, when this binding is disrupted, the signal transduction pathway is disrupted, making this binding interaction a useful target for cancer therapy. Therefore, the present specification provides sufficient enablement for the presently claimed method.

The Examiner states that she has considered applicants' previous arguments but does not find them persuasive. As noted above, applicants have more clearly defined the APB domain which binds to an APB recognition region, and as such more clearly sets forth the APB recognition regions that bind to the APB domain. Applicants believe that the specific recitation of the APB domain overcomes the Examiner's bases for the rejection.

Applicants do not agree with the Examiner that the ability to screen compounds for a desired activity is an invitation to experiment. Applicants respectfully disagree and again direct the examiner's attention to a heading entitled "Identification of APB Modulating or Binding Agents" on page 29, line 16 of the specification. It is submitted that this section is highly probative of enablement and directly refutes the examiner's contentions. This section describes affinity binding methods wherein an APB domain containing protein is exposed to

various potential binding agents and those showing binding affinity are isolated and characterized according to routine methods in the art. For example, on page 31, lines 3-9 of the specification it states:

> *Molecules exhibiting binding activity may be further screened for an ability to effect APB binding or modulate APB mediated activity. For example, the molecule can be tested for its ability to increase or decrease APB binding. Alternatively, the molecule may be tested for its ability to increase or decrease one or more activities mediated by the APB domain protein.*

The specification continues with a discussion of alternative assays that can be used to identify compounds that can be used in the methods of the invention. Such assays include *in vitro* complex formation (page 31, line 12) and co-immunoprecipitation techniques well known to those of ordinary skill in the art (page 31, lines 24-25). Additional detailed methodologies are found on page 32, lines 7 et seq. for identifying compounds that can be used in the claimed methods.

Because the methods of the invention can take many forms including using therapeutic peptides, there is further discussion, beginning page 34 and again on page 52, of gene therapy techniques that can be employed using peptides that display activity against APB domain containing proteins. The Examiner is reminded that [t]he test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The above discussion illustrates that the present specification provides enablement for the presently claimed method for altering signal transduction in an APB domain-containing signal transduction pathway. Therefore, the present claims comply with the requirements of 35 U.S.C. § 112, first paragraph.

New Grounds of Rejection

Claims 26-32 and 35 are rejected by the examiner under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification as filed, because claim 26 recited the APB domain with " at least 80% sequence identity to the APB domain present in Shc or at least 75% similiarity to the APB domain in Shc." Applicants have corrected this typographical error and have amended claim 26 to recite "...75% simililarity..." and "...80% identity..." It is believed that this claim amendment obviates this rejection and its withdrawal is requested.

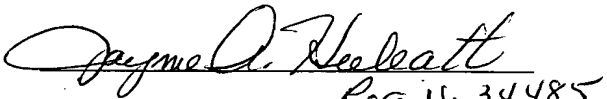
CONCLUSION

Entry of the present amendment is respectfully requested. The amendments to the claims clarify the claim language, reduce issues for appeal and do not raise new issues. As the above-presented amendments and remarks address and overcome all of the rejections presented by the Examiner, withdrawal of the rejections and allowance of the claims are respectfully requested.

If the Examiner has any questions concerning this application, he or she is requested to contact the undersigned.

Respectfully submitted,

Date February 3, 2003

By 
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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

26. (Amended) A method for altering signal transduction in an APB domain-containing signal transduction pathway comprising administering to a patient a therapeutically effective amount of [an] **a therapeutic** agent which decreases binding between an APB recognition region present in a first protein and an APB domain present in a second protein, wherein said APB domain shares at least [80%] **75%** sequence similarity or at least [75%] **80%** sequence identity with the APB domain present in [Shc] **amino acids 46-209 of $p52^{shc}$ as set forth in SEQ ID NO:2**.

31. (Amended) The method of claim 26, wherein said first protein is a receptor tyrosine kinase [and said second protein is Shc].